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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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MILLEN, WHITE, ZELANO & BRANIGAN, PC
2200 CLARENDON BLVD
SUITE 1400
ARLINGTON, VA 22201

EXAMINER	
DUFFY, PATRICIA ANN	

ART UNIT	PAPER NUMBER
1645	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/078,531	MARTIN ET AL.	
	Examiner	Art Unit	
	Patricia A. Duffy	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 July 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-45* is/are pending in the application.

4a) Of the above claim(s) *1-16,22-29 and 31-34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17-21,30 and 35-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 May 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: Sequence Listing Alignments -2

500

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7-11-05 has been entered.

Claims 1-45 are pending. Claims 17-21, 30, 35-45 are under examination. Claims 1-16, 22-29, 31-34 are withdrawn from consideration as drawn to non-elected inventions.

The examiner in charge of this application has changed. Please address all future correspondence to Exr. Patricia A. Duffy, Art Unit.

The rejections of record are withdrawn in favor of the new grounds of rejection set forth below. The objection to the drawings is withdrawn in view of the replacement drawings submitted 5-20-05.

Priority

Applicant's claim for domestic priority under 35 U.S.C. 119(e) to 60/269,840 is acknowledged. However, the provisional application upon which priority is claimed fails to provide adequate support under 35 U.S.C. 112 for claims 17-21, 30, and 35-45 of this application. This application has been examined in light of the instant filing date of 2-21-05.

Specification

The use of the trademarks has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent

their use in any manner which might adversely affect their validity as trademarks. Failure to correct this in the next office action will be considered non-responsive.

Drawings

The replacement drawing filed 5-20-04 have been entered into the record and approved by the examiner.

Double Patenting

Claims 17-21 and 30 of this application conflict with claims 17-21 and 30 of Application No. 10078,531. 37 CFR 1.78(b) provides that when two or more applications filed by the same applicant contain conflicting claims, elimination of such claims from all but one application may be required in the absence of good and sufficient reason for their retention during pendency in more than one application. ***Applicant is required to either cancel the conflicting claims from all but one application or maintain a clear line of demarcation between the applications. See MPEP § 822.***

Claims 17-21 and 30 provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 17-21 and 30 of copending Application No. 10/476,614. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 17-21, 30, 35-45 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The claims have been amended such that the variant "elicits antibodies specific for BVH-P7 of *S. pyogenes*. The limitation does not appear to have explicit written description in the specification as filed. As such, this limitation is deemed new matter at this time. This issue is best resolved by Applicant pointing to the specification by page and line number where written description support for the now claimed invention can be found. Applicants should also point to the specification by page and line number where the limitation of antibody in relation to the claimed chimeric is disclosed.

Claims 17-21, 30, 35-45 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The teachings of the specification are limited to isolated polypeptides that are naturally occurring variants from *S. pyogenes* having 95% identity as compared to the full-length of the polypeptide set forth in SEQ ID NO:2. The teaching of the specification are also limited to a leader peptide consisting of amino acid residues 1-21 of SEQ ID NO:2. the specificaiton does not teach the leader peptides of the other disclosed naturally occurring variants. The specification also broadly describes "BVH-P7 protein" specifically, by reference to the polynucleotide sequence of SEQ ID NO:2 (see page 3 of specification description of Figure 2). The specification also broadly describes the invention as embracing any non-natural substitution, insertion or deletion change of nucleotides throughout the entire stretch of amino acids found in the polypeptide set forth in SEQ ID NO:2 or fragments or epitopes thereof (see pages 8-10). These sequences correspond to sequences from other bacterial species, mutated sequences and non-natural variants and epitopes or fragments that have no written description in the specification as filed. As such, these non-natural sequences, variants less than 95% identical, epitopes, lacking leader/signal/secretory amino acid sequences The specification fails to teach the signal peptide for any of the naturally occurring variants and does not teach the N-terminal sequence is a methionine. Therefore, none of these claimed polypeptide sequences meets the written description provision of 35 U.S.C. 112, first paragraph. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.).

The claims are drawn a polypeptide with a recited percent identity that elicits antibodies specific for BVH-P7 of *S. pyogenes.* The specification does not define BVH-P7 from *S. pyogenes.* The specification teaches a single nucleic acid (SEQ ID NO:1) encoding

a "BVH-P7" polypeptide of SEQ ID NO:2 that was demonstrated to bind antibodies of animals immunized with the homologous strain or random individuals. The specification does not place any structure, chemical or functional limitations on the recited BVH-P7. The recitation of "BVH-P7" does not convey a common structure or function. The scope of the claims includes numerous structural variants, and the genus is highly variant because a significant number of structural differences between genus members is permitted. Although the specification teaches that variants can be readily screened, the specification and the claim do not provide any guidance on the structure of the polypeptide and what non-natural changes can or can not be made. Structural features that could distinguish compounds in the genus from others in the protein class are missing from the disclosure and the claims. No common structural attributes identify the members of the genus that elicit antibodies that bind a structurally undefined protein or chemical. The general knowledge and level of skill in the art do not supplement the omitted description, because specific, not general guidance is needed. Since the disclosure fails to describe the common attributes or structural characteristics that identify members of the genus, and because the genus is highly variant, the function of the binding of antibody alone is insufficient to describe the genus of BVH-P7 polypeptides of that function equivalently. One of skill in the art would reasonable conclude that the disclosure of natural sequences that are 95% identical to each other, fails to provide a representative number of species to describe the claimed genus of 90% or 70% identical and non-natural variants. Applicants were not in possession of the claimed genus of non-natural variants because the specification does not convey to one of skill in the art a representative number of variants in structure and function of any such polypeptide that has the claimed/structure and function. The genus of polypeptides with the claimed function is substantial and highly variant because the polypeptides do not have a common structure and function. The recitation of "BVH-P7" does not convey a common structure nor a common function. As such, generic non-natural polypeptide sequences that are unrelated via structure and

function are highly variant and not conveyed by way of written description by the specification at the time of filing. As such the specification lacks written description for the highly variant genus of single function polypeptides (antibody binding) and one skilled in the art would not recognize that applicants had possession of the genus of claimed polypeptides for use in the assay as instantly claimed or for therapy. As to embodiments reciting fragments or epitopes or secretory sequences. The specification as filed does not teach the secretory sequence for any of the other disclosed naturally occurring variants. The specification as filed does not teach either B-cell or T-cell epitopes of SEQ ID NO:2 or identify any naturally occurring fragments of SEQ ID NO:2. The specification as filed does not identify any conserved or non-conserved immunodominant epitopes by conventional epitope mapping with antibodies or by any other method. As such, the specification fails to convey possession of isolation of polypeptides or fragments comprising epitopes. . The courts have held that it is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. (Genentech Inc. v. Novo Nordisk A/S Ltd., 42 USPQ2d 1001). Moreover, the specification must have been enabling at the time the invention was made and developments after the time of filing are of no consequence to what one skilled in the art would have believed at the time of filing (*In re Wright*, 27 USPQ2d 1510). In the absence of a teaching of the claimed polypeptides are effective in prevention of disease, the specification is not be enabled for cross-protective vaccines, vaccines comprising fragments, epitopes, chimerics or any variants of SEQ ID NO:2. In view of the unpredictability of the art, the lack of teachings of the specification, it would require undue experimentation on the part of the skilled artisan to practice the invention as claimed. Applicants propose that the skilled artisan is to modify a known a known protein sequence and that modification would still describe applicants' invention as a BVH-P7 protein as disclosed. The BVH-P7 protein, disclosed as SEQ ID NO:2, has no known correlation to any other proteins in the art. The specification fails to teach the structure

or relevant identifying characteristics of a representative number of species of a representative number of proteins, sufficient to allow one skilled in the art to determine that the inventor had possession of the genus invention as claimed (i.e. non-natural variants at least 70% , 90% or 95% identical as compared to SEQ ID NO:2 or a fragment or epitope thereof. The specification fails to provide a representative number of protein variants to indicate that applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the limited disclosure of full length SEQ ID NO:2 and naturally occurring variants that are at least 95% identical. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, 1483. In Fiddes v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class.

Therefore, only an isolated polypeptide from *S. pyogenes* having at least 95% identity to the full-length of the amino acid sequence set forth in SEQ ID NO:2, an isolated polypeptide comprising the amino acid sequence as set forth in SEQ ID NO:2, lacking leader sequence consisting of amino acid residues 1 to 21 of SEQ ID NO:2 or an isolated polypeptide of SEQ ID NO:2 or pharmaceutical compositions comprising SEQ ID NO:2, SEQ ID NO:2 lacking the leader sequence or SEQ ID NO:2 wherein the N-terminal methionine residues is deleted, meets the written description provision of 35 U.S.C. 112, first paragraph. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision. (See page 1115.)

Applicants' arguments have been carefully considered but are not persuasive. No fragments or epitopes are taught by this specification. No non-natural variants are taught by this specification. Applicants' mere regurgitation of any amino acid can be

conservatively changed or changed is not a teaching of a representative number variants to demonstrate possession of the full-breadth of the claimed genus. Applicants must show conception by way of written description with a representative number of species that allow one skilled in the art to ascertain that Applicant was in possession of the necessary structural and functional aspects of the claimed genus. Here Applicants have not demonstrated possession of fragments, epitopes, non-natural variants that have the claimed or contemplated functions or naturally occurring variants having at least 70% or at least 90% identity.

Claims 17-21, 30, 35-45 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for isolated polypeptide from *S. pyogenes* having at least 95% identity to the full-length amino acid sequence as set forth in SEQ ID NO:2, an isolated polypeptide comprising the amino acid sequence as set forth in SEQ ID NO:2 lacking the leader sequence consisting of amino acid residues 1 to 21 of SEQ ID NO:2 or an isolated polypeptide of SEQ ID NO:2 wherein the N-terminal methionine residues is deleted and pharmaceutical compositions comprising an isolated polypeptide of SEQ ID NO:2 lacking the leader sequence consisting of amino acid residues 1 to 21 of SEQ ID NO:2 or an isolated polypeptide comprising the amino acid sequence as set forth in SEQ ID NO:2 wherein the N-terminal methionine residues is deleted, it does not reasonably provide enablement for polypeptides comprising 10 contiguous amino acids, chimerics, multimers or epitopes or at least 70%, 90% variants, and non-natural variants of polypeptides that are at least 95% identical with a fragment or the full length of SEQ ID NO:2, chimerics or multimers thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are drawn to and encompass polypeptides which comprise a sequence which has a recited percent identity or average variability as compared to a nucleotide sequence of SEQ ID NO:2, fragments at least 10 contiguous amino acids, and epitopes and chimeric thereof. These claims are not enabled for the following reasons. The written description for a full-length protein is limited to only naturally occurring variants of at least 95% identity with the full length SEQ ID NO:2, and specific fragments of SEQ ID NO:2, lacking amino acids 1-21 or lacing the N-terminal methionine. The specification fails to teach any fragments or epitopes that elicit antibodies specific for BVH-P7 of *S. pyogenes* and further lacks any description of any variants thereof. The specification is also not enabled for the claimed non-naturally occurring variants or any variants that are

at least 70% or 90% identical to SEQ ID NO:2 or any fragment thereof, because 1) the specification fails to teach where and how much variation of SEQ ID NO:2 is permitted such that the polynucleotide sequence or protein sequence encoded thereby is still able to function as claimed ,is able to produce antibodies specific for BVH-P7 of *Streptococcus pyogenes or* as a diagnostic or therapeutic as asserted specification; 2) the specification lacks any written description of any fragments of at least 10 contiguous amino acids or epitopes of SEQ ID NO:2 as claimed which are capable of functioning as a therapeutic or diagnostic as asserted in the specification which are encompassed by the comprising language of the claims; 3) the specification fails to teach how to use nucleic acid sequences which are variants of SEQ ID NO:1 to produce variants useful in to produce chimerics in the diagnosis or detection because the specification fails to teach what are the critical nucleic acid residues that can be modified and still achieve a nucleic acid that will function as a diagnostic or detection reagent for *Streptococcus pyogenes;* 5) the art teaches that polynucleotides isolated based on percent homology do not predictably display the functions of their homologs and one skilled in the art would have reason to doubt the assertion that SEQ ID NO:2 has the ability to act as a diagnostic or therapeutic reagent; 6) the art teaches that even replacement of a single amino acid residue may lead to both structural and functional changes in biological activity and immunological recognition of a protein, one skilled in the art would have reason to doubt the validity and functionality of for therapeutic use or diagnostic use of variants or chimerics thereof; and 7) the specification has not displayed a nexus between the structure of the polypeptide and function of the protein to elicit antibodies specific for BVH-P7 as either a protein with detection or diagnostic use.

As to points 1)- 7), the specification fails to provide a written description of any leader/signal/secretory sequence of any of the disclosed natural variants that are at least 95% identical as compared to the full length of the amino acid sequence set forth in SEQ ID NO:2, which function equivalently to a polypeptide comprising the disclosed SEQ ID

NO:2, are able to be used as a diagnostic/detection reagent or are therapeutic/vaccine agents. The specification fails to teach the critical protein residues involved in the function of the protein SEQ ID NO:2 as a diagnostic or therapeutic, such that the skilled artisan is provided no guidance to test, screen or make non-natural sequence of the polypeptide of comprising SEQ ID NO:2, using conventional technology which allow for a screening or generic diagnostic or therapeutic use asserted in the specification. The specification fails to teach to what extent you could alter SEQ ID NO:2 and still present the sequence as diagnostic or therapeutic. In order to be diagnostic the sequence must distinguish *Streptococcus pyogenes* from non-pathogenic *Streptococcal* sp. and other clinically relevant autochthonous bacteria in a host. In order to be therapeutic, the dictionary definition of vaccine (i.e. the instant pharmaceutical composition) is "A prophylactic or therapeutic material containing antigens derived from one or more pathogenic organisms which, on administration to man or animal, will stimulate active immunity and protect against infection with these or related organism (i.e. produce protective immunity)." (The Dictionary of Immunology, Herbert et al eds, Academic Press, 1995) would clearly realize the critical deficiency of this specification with respect to fragments, chimerics and variants for vaccines. The term pharmaceutical composition is defined in the specification as treatment of prophylaxis (i.e. prevention) of disease for the genus *Streptococcus* (see page 15 of the specification). There is absolutely no demonstration of cross-strain or cross genus protective immunity upon administration of SEQ ID NO:2 or any claimed variant, fragment or chimeric thereof in any animal model of Streptococcal disease. Such is required by the common meaning as demonstrated by the dictionary definition. No art recognized homologs have identified or have been demonstrated to have vaccine properties with the homologous or heterologous microorganism. The art is replete with evidence that the ability to produce an antibody (immunogenicity) is insufficient to correlate with protection from infection. See for example Feng et al (Infection and Immunity, 64(1):363-365, 1996) that teaches that P55,

is an immunogenic but nonprotective 55-kilodalton *Borrelia burdorferi* protein in murine lyme disease. As such, one skilled in the art would have ample reasons to doubt the ability to use the claimed composition comprising the polypeptide and fragments thereof as a vaccine. The teachings of the specification are devoid of any teaching that animals in a normal infection generate antibodies that bind the polypeptide(s) variants that are claimed and therefore is not clear that the polypeptides of the invention are capable of generating an antibody response during a normal course of infection that is protective. The teachings of the specification are limited to SEQ ID NO:2, and homologous protection (see page 35, Example 8 of the specification). Further, the specification fails to teach that any immune response generated upon injection by the claimed 95% variant polypeptides or fragments of SEQ ID NO:2, unidentified epitopes thereof, alone or in combination with other fragments or epitopes provide for a protection against the same strain, variant serotypes or genotype (i.e. Streptococcal) infection . Vaccines by definition trigger an immunoprotective response in the host vaccinated and mere antigenic response is insufficient. Therefore, merely because the protein can elicit antibodies specific for BVH-P7, which is not structurally defined in the claim, or against themselves, there is no expectation that these antibodies will also be protective, because the specification does not disclose the protective epitopes or demonstrate cross-strain protection. It is well recognized in the vaccine art, that it is unclear whether an antigen(s) derived from a pathogen will elicit protective immunity. Ellis, R.W. (Chapter 29 of "VACCINES" [Plotkin, S.A. et al. (eds) published by W. B. Saunders company (Philadelphia) in 1988, especially page 571, 2nd full paragraph] exemplifies this problem in the recitation that "The key to the problem (of vaccine development) is the identification of that protein component of a virus or microbial pathogen that itself can elicit the production of protective antibodies.... and thus protect the host against attack by the pathogen". The specification fails to teach even one of the claimed variant polypeptides, fragments, epitopes or chimerics thereof alone or in combination with other antigens does in fact confer protection from

infection, as is requisite of a vaccine composition. The art teaches that the selection of protective antigens from the plethora of protein antigens available is unpredictable. The specification fails to teach that the claimed epitope, fragment or chimeric is able to perform as a vaccine (i.e. protection, reduction in morbidity and/or mortality of disease) and the art does not recognize any homologs or other similar proteins, fragments or chimerics as a vaccines. One of skill in the art would be reduced to merely randomly altering amino acids which would lead to unpredictable results regarding the functional activity of the polypeptide to be used as a diagnostic reagent, detection reagent or therapeutic agent. Moreover, protein chemistry is probably one of the most unpredictable areas of biotechnology and the art teaches that the significance of any particular amino acid and sequences for different aspects of biological activity can not be predicted *a priori* and must be determined empirically on a case by case basis (Rudinger et al, in "PEPTIDE HORMONES", edited by Parsons, J.A., University Park Press, June 1976, page 6). The art specifically teaches that even a single amino acid change in a protein leads to unpredictable changes in the biological activity of the protein. For example, replacement of a single lysine residue at position 118 of the acidic fibroblast growth factor by glutamic acid led to a substantial loss of heparin binding, receptor binding, and biological activity of the protein (Burgess et al., The Journal of Cell Biology, 111:2129-2138, 1990). In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine, or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biologic activity of the mitogen (Lazar et al., Molecular and Cellular Biology, 8(3):1247-1252, 1988). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification, will often dramatically affect the biological activity of a protein. Proteins with replacement of a single amino acid residues may lead to both structural and functional changes in biological activity and immunological recognition. For example, Jobling et al. (Mol. Microbiol., 1991, 5(7):1755-67 teaches a panel of single amino acid substitutions by oligonucleotide directed

mutagenesis which products proteins that differ in native conformation, immunological recognition, binding and toxicity, thus exemplifying the importance of structural components to both biological function and immunological recognition. The specification has not taught which residues of SEQ ID NO:2 can be varied and still achieve a protein that is functional as a therapeutic or is capable of use as a diagnostic using immunological means of recognition. Since, the specification lacks a written description of any fragment, epitope or chimeric thereof which has the ability to function as claimed or as a therapeutic or detection reagent, it is not enabled for this language because it fails to enable the skilled artisan to envision the detailed chemical structure of the non-natural variants or 70-90% variants of SEQ ID NO:2 that functions as alleged, respectively, as well as the screening method of obtaining them, as well as how to use the protein variants. The teachings of the specification fail to allow one skilled in the art to predict what effect a given change in the amino acid sequence will cause with respect to the claimed function, diagnostic or therapeutic functions. The protein has specific immunological and biological properties which are the result of its primary acid sequence as encoded by this nucleic acid sequence. Applicants' proposed insertions, deletions or substitutions to that sequence do not predict a protein having all the identifiable properties of the protein set forth as SEQ ID NO:2 as disclosed. The skilled artisan would be forced into undue experimentation to make and use the instantly claimed scope of invention. Although the skilled artisan might envision making a great number of changes of a reference polypeptide in accordance with applicant's disclosure, it is unclear exactly that the protein would diagnose, detect, vaccinate or treat *Streptococcus or Streptococcus pyogenes* infection. These altered polypeptides which would vary from the disclosed natural protein sequences in some unknown or unpredictable manner. *Amgen Inc. v. Chugai Pharmaceutical Co. Inc.* 18 USPQ2d 1016, 1026 (CAFC 1991) addressed a similar issue of enablement and undue experimentation for analogs of erythropoietin (EPO) gene broadly claimed and narrowly disclosed. In that instance, it was found:

that over 3,600 different EPO analogs can be made by substituting at only a single amino acid position, and over a million different analogs can be made by substitution three amino acids. The patent indicates that it embraces means for preparation of "numerous" polypeptide analogs of EPO. Thus, the number of claimed DNA sequences encoding sequences that can produce EPO-like product is potentially enormous.

Further, at page 1027, the CAFC found that:

it is not necessary that a patent applicant test all the embodiments of his invention, ... what is necessary is that he provide a disclosure sufficient to enable one skilled in the art to carry out the invention commensurate with the scope of the claims. For DNA sequences, this means disclosing how to make and use enough sequence to justify a grant of the claims sought. Amgen has not done that here. In addition, it is not necessary that a court review all of the *Wands* factors to find a disclosure enabling. They are not illustrative, not mandatory. What is relevant depends on the facts, and the facts here are that Amgen has not enabled preparation of DNA sequences to support its all-encompassing claims... Here, however, despite extensive statements in the specification concerning all the analogs of the EPO gene that can be made, there is little enabling disclosure of particular analogs and how to make them. Details for preparing only a few EPO analogs genes are disclosed. Amgen argue that this is sufficient to support its claims; we disagree. This "disclosure" might well justify a generic claim encompassing these and similar analogs, but it represents inadequate support for Amgen's desire to claim all EPO analogs. There may be other genetic sequence that code for EPO-Type products. Amgen has told how to make and use only a few of them and is therefore not entitled to claim all of them...[W]e do not intend to imply that genetic sequences cannot be valid where they are of a scope appropriate to the invention disclosed by an applicant. That is not the case here, where Amgen has claimed every possible analog of a gene

containing about 4,000 nucleotides, with a disclosure of hot to make EPO and a very few analogs.

Finally, at page 1028, the CAFC concludes:

> Considering the structurally complexity of the EPO gene, the manifold possibilities for change in its structure, with an attendant uncertainty as to what utility will be possessed by these analogs, we consider that more is needed concerning identifying the various analogs that are within the scope of the claim, methods for making them, and structural requirements for producing compounds with EPO-like activity. It is not sufficient, having made the gene and a handful of analogs whose activity has not been clearly ascertained, to claim all possible genetic sequences that have EPO-like activity. Under the circumstances, we find no error in the court's conclusion that generic DNA sequence claims are invalid under section 112.

See also *In re Duel* 34 USPQ2d 1210 (CAFC 1995); *Colbert v. Lofdahl* 21 USPQ2d 1068 (Bd. Pat. Ap. Inter. 1991); and *University of California v. Eli Lilly and Co.* 43 USPQ2d 1398 (CAFC 1997).

In view of the lack of written description of the entire scope of variants, fragments and epitopes as claimed, the lack of working examples commensurate in scope with the instant claims to demonstrate cross-strain, genus or homologus protection using variants, fragments chimeric etc, that one skilled in the art would be unable to practice the invention as broadly claimed.

Applicants' arguments have been carefully considered but are not persuasive in view of the lack of written description of diagnostically useful or protective epitopes or fragments. Further, as set forth above mere antibody binding or the ability to elicit

antibodies to self does not provide for a protective or diagnostically relevant epitope that is either discriminatory or genus specific.

Claim 17, 18, 21, 30, 35-40, 42-45 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

As to claim 17, embodiment (f) is indefinite inasmuch as none of the (a)-(e) are required to have an N-terminal methionine and as such, it is unclear how one can define the deletion of something that is not necessarily present. As to claim 17, embodiment (g), the term "the secretory amino acid sequence" is prima facie indefinite because it is not defined in the claims and therefore lacks clear antecedent basis. As such, the claims are indefinite.

Claim 18, embodiments (f) and (g) have the same issue as recited above. Claim 43,44 and 45 have the same issues as claim 17 above.

Claims 21, 30, 35-40 and 42 are indefinite as depending from indefinite claims.

As to claims 43-45 as lacking proper antecedent basis in claim 1 and depend from a non-elected invention. In order to advance prosecution, these claims have been examined as if they were dependent upon claim 17.

As to claim 42, the claim is prima facie indefinite because a polypeptide cannot functionally hybridize to a nucleic acid. The claim is also indefinite because neither the specification nor the claims define stringent conditions.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 17, 18, 19, 35 and 36 are rejected under 35 U.S.C. 102(b) as anticipated by Dixon et al, PIR_79 Database Accession Number T51594, Dixon et al, August 18, 2000.

Dixon et al teach a polypeptide comprising residues 133-141 that is 100% identical to an epitope of SEQ ID NO:2 amino acid residues 929-937. Since, neither the specification nor the claims provide the metes and bounds of the claimed epitopes, the sequence of the prior art inherently meets this limitation.

Claims 17, 18, 19, 35 and 36 are rejected under 35 U.S.C. 102(b) as anticipated by McDonald on et al, PIR_79 Database Accession Number JE0176, July 03, 1998.

McDonald et al teach a polypeptide comprising residues 174-182 that is 100% identical to an epitope of SEQ ID NO:2 amino acid residues 592-600. Since, neither the specification nor the claims provide the metes and bounds of the claimed epitopes, the sequence of the prior art inherently meets this limitation.

Claims 17, 18, 19, 35-45 are rejected under 35 U.S.C. 102(a) as being anticipated by Ferretti et al (PNAS, 98(8):4658-4663, April 10, 2001).

Ferretti et al teach the complete genome sequence of an M1 strain of *Streptococcus pyogenes* and all the open reading frames encoding proteins. Ferretti et al teach a polypeptide sequence that is 100% identical as compared to SEQ ID NO:2. As

such, the polypeptide of the prior art anticipates the instantly claimed invention (see attached alignment).

Claims 17, 18, 19, 20, 21, 30, 35-39, 41, 42 and 43 are rejected under 35 U.S.C. 102(a) as being anticipated by Le Page et al (WO 01/32882, published May 19, 2001).

LePage et al teach a polypeptide that is 74.4% identical as compared with SEQ ID NO:2 (see alignment). The polypeptide comprises multiple fragments of at least 10 consecutive amino acids from SEQ ID NO:2 connected by heterologous amino acids and therefore represents a chimeric polypeptide (see attached alignment). LePage et al also teach epitopes of SEQ ID NO:2. LePage et al teach vaccines comprising the proteins in a pharmaceutically acceptable carrier (see pages 39-40). LePage et al contemplated peptides and fragments of the disclosed sequences (page 4) As such, LePage anticipate the invention.

Status of the Claims

All claims stand rejected.

Conclusion

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia A. Duffy whose telephone number is 571-272-0855. The examiner can normally be reached on M-Th 6:30 am - 6:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on 571-272-0864.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Patricia A. Duffy, Ph.D.

Primary Examiner

Art Unit 1645